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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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(54) Title: STABLE CARPROFEN COMPOSITION

(57) Abstract: A stable solvent-based composition is described which is particularly useful in warm blooded animals such as dogs. The composition comprises a therapeutically effective amount of carprofen, one or more polyols, one or more stabilising agents and optionally, one or more co-solvents.

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STABLE CARPROFEN COMPOSITION

Technical Field

This invention relates to non-steroidal anti-inflammatory drug (NSAID) compositions and in particular to such compositions where the NSAID is presented in the form of a solution for use in warm blooded animals, such as dogs.

Background Art

There are a number of NSAID's that are known to be useful for the treatment of inflammation and pain in animals such as dogs. These NSAID's are typically used in treating postoperative pain associated with soft tissue and orthopaedic surgeries as well as for the relief of pain and inflammation associated with osteoarthritis.

One such useful NSAID is carprofen. This drug is a member of the class of drugs that includes indomethacin, naproxen and ketoprofen. Chemically, carprofen is 6-chloro-α-methyl-9H-carbazole-2-acetic acid.

Whilst carprofen has been found to be very effective therapeutically, in order to maintain an acceptable stability profile, it must be formulated in dosage forms such as tablets where solvents are largely excluded. For administration to humans, such dosage forms do not present a barrier to use. However, for administration to non-human animals, solid dosage forms are not well tolerated and are generally difficult to administer.

It would therefore be desirable if carprofen could be presented in a non- solid dosage form thereby allowing the substance to be more easily administered.

The present inventors have recognised this limitation on the use of carprofen and accordingly have sought to provide compositions that are stable and solvent-based for ease of administration to warm-blooded animals, especially dogs.

In the disclosure that follows, any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is solely for the purpose of providing a context for the present invention. It is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed before the priority date of each claim of this application.

Moreover, throughout this specification the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

Summary of the Invention

The present inventors have achieved stable solvent-based compositions of carprofen through the finding that certain solvent combinations with carprofen result in formulations that are stable and are suitable for oral administration to animals.

Accordingly, in a first aspect, the present invention is directed to a stable solvent-based composition comprising:
a therapeutically effective amount of carprofen;
one or more polyols;
one or more stabilising agents; and optionally,
one or more co-solvents.

In a second aspect, the present invention is further directed to a method of treating pain and/or inflammation in a warm-blooded non-human animal, the method comprising administering to the animal a therapeutically effective amount of carprofen which is solubilised in a composition which comprises:
one or more polyols;
one or more stabilising agents; and optionally,
one or more co-solvents.

In a third aspect, the present invention is further directed to the use of a composition which comprises:
one or more polyols;
one or more stabilising agents; and optionally,
one or more co-solvents,
to stabilise carprofen and to facilitate the oral administration of a therapeutically effective amount of carprofen to a warm-blooded non-human animal.

In a fourth aspect, the present invention is still further directed to use of a therapeutically effective amount of carprofen which is solubilised in a composition which comprises:
one or more polyols;
one or more stabilising agents; and optionally,
one or more co-solvents.
in the preparation of a medicament for treating pain and/or inflammation in a warm-blooded non-human animal.

Preferably, carprofen is included in the composition in an amount of about 1 to 500g/L, more preferably about 5 to 50 g/L, even more preferably about 20 to 50g/L. At these concentrations, an appropriately therapeutically effective amount of the composition may be administered to an animal.

One or more polyols are included in the composition and these may be selected from the group consisting of propylene glycol, glycerol, sorbitol, solid polyethylene glycols, liquid polyethylene glycols and mixtures of the foregoing. Broadly the polyols may be incorporated in an amount of from about 20 to 998g/L. Preferably they are used in an amount of from about 700 to 998g/L. In the case of sorbitol, it is usual to provide the sorbitol as a 70% w/v aqueous solution. In addition, in order for the polyethylene glycols to be liquid, there molecular weight will generally be in the range of about 300-600. However, potentially solid polyethylene glycols could be used in combination with one or more suitable co-solvents.

Amongst the stabilising agents that may be used are antioxidants. These include α tocopherol and salts thereof, ascorbic acid and salts thereof, methoxyphenol and derivatives thereof, trihydroxybenzoate and derivatives thereof, hydroquinone and derivatives thereof, methyl phenol and derivatives thereof and sodium metabisulfite. Generally these stabilising agents are regarded as antioxidants. In addition, benzyl alcohol may be used as a stabilising agent. Such stabilising agents may be used singly or in combination in a total amount of about 0.1 to 50 g/L, preferably about 10 to 20g/L.

Optionally, one or more co-solvents may be included in the compositions of the invention. One co-solvent that may be used is ethanol. If a co-solvent is used, the amount is typically up to about 500g/L, preferably about 10 to 300g/L.

Although the compositions of the invention are solutions of carprofen, it will be readily appreciated that the viscosity of such solutions may be modified to produce compositions that are enhanced so as to be, for example, more paste like or in the form of a gel.

To produce the compositions of the invention, the carprofen may be dissolved in polyol along with the stabilising agent. If a co-solvent is used, it may be added following the dissolution of the carprofen and stabilising agent.

The compositions according to the present invention are for oral administration to warm-blooded animals, particularly dogs. For successful administration, these compositions must be palatable to the animal to be treated.

In a preferred embodiment according to the first aspect of the invention, there is provided a stable solvent-based composition comprising:

a therapeutically effective amount of carprofen in an amount of about 1 to 500g/L;

one or more polyols in an amount of from about 20 to 998g/L;

one or more stabilising agents in an amount of from about 0.1 to 50g/L; and

one or more co-solvents in an amount of from about 0 to 500g/L.

In an even more preferred embodiment according to the first aspect of the invention, there is provided a stable solvent-based composition comprising:

a therapeutically effective amount of carprofen in an amount of about 1 to 500g/L;

one or more polyols in an amount of from about 20 to 998g/L, wherein the one or more polyols are selected from the group consisting of propylene glycol, glycerol, sorbitol, solid polyethylene glycols and liquid polyethylene glycols and mixtures of the foregoing;

one or more stabilising agents in an amount of from about 0.1 to 50g/L, wherein the one or more stabilising agents are selected from the group consisting of α tocopherol and salts thereof, ascorbic acid and salts thereof, methoxyphenol and derivatives thereof, trihydroxybenzoate and derivatives thereof, hydroquinone and derivatives thereof, methyl phenol and derivatives thereof, sodium metabisulfite and benzyl alcohol; and

a co-solvents in an amount of from about 0 to 500g/L, wherein the co-solvent is ethanol.

In a preferred embodiment of the second aspect of the invention, there is provided a method of treating pain and/or inflammation in a warm-blooded non-human animal, the method comprising administering to the animal a therapeutically effective amount of carprofen in an amount of about 1 to 500g/L which is solubilised in a composition which comprises:

one or more polyols in an amount of from about 20 to 998g/L, wherein the one or more polyols are selected from the group consisting of propylene glycol, glycerol, sorbitol, solid polyethylene glycols and liquid polyethylene glycols and mixtures of the foregoing;

one or more stabilising agents in an amount of from about 0.1 to 50g/L, wherein the one or more stabilising agents are selected from the group consisting of α tocopherol and salts thereof, ascorbic acid and salts thereof, methoxyphenol and derivatives thereof, trihydroxybenzoate and derivatives thereof, hydroquinone and derivatives thereof, methyl phenol and derivatives thereof, sodium metabisulfite and benzyl alcohol; and

a co-solvents in an amount of from about 0 to 500g/L, wherein the co-solvent is ethanol.

In a preferred embodiment of the third aspect of the invention, there is provided use of a composition which comprises:

one or more polyols in an amount of from about 20 to 998g/L, wherein the one or more polyols are selected from the group consisting of propylene glycol, glycerol, sorbitol, solid polyethylene glycols and liquid polyethylene glycols and mixtures of the foregoing;

one or more stabilising agents in an amount of from about 0.1 to 50g/L, wherein the one or more stabilising agents are selected from the group consisting of α tocopherol and salts thereof, ascorbic acid and salts thereof, methoxyphenol and derivatives thereof, trihydroxybenzoate and derivatives thereof, hydroquinone and derivatives thereof, methyl phenol and derivatives thereof, sodium metabisulfite and benzyl alcohol; and optionally,

a co-solvents in an amount of from about 0 to 500g/L, wherein the co-solvent is ethanol;

to stabilise carprofen and to facilitate the oral administration of a therapeutically effective amount of carprofen in an amount of about 1 to 500g/L to a warm-blooded non-human animal.

In a preferred embodiment of the fourth aspect of the invention, there is provided use of a therapeutically effective amount of carprofen in an amount of about 1 to 500g/ which is solubilised in a composition which comprises:

one or more polyols in an amount of from about 20 to 998g/L, wherein the one or more polyols are selected from the group consisting of propylene glycol, glycerol, sorbitol, solid polyethylene glycols and liquid polyethylene glycols and mixtures of the foregoing;

one or more stabilising agents in an amount of from about 0.1 to 50g/L, wherein the one or more stabilising agents are selected from the group consisting of α tocopherol and salts thereof, ascorbic acid and salts thereof, methoxyphenol and derivatives thereof, trihydroxybenzoate and derivatives thereof, hydroquinone and derivatives thereof, methyl phenol and derivatives thereof, sodium metabisulfite and benzyl alcohol; and optionally,

a co-solvents in an amount of from about 0 to 500g/L, wherein the co-solvent is ethanol;

in the preparation of a medicament for treating pain and/or inflammation in a warm-blooded non-human animal.

Brief description of the figures

Figure 1 is a comparison of the average carprofen concentration versus time profile between a stable liquid composition according to the present invention and Rimadyl® tablets.

Modes for Carrying out the Invention

In order to better understand the nature of this invention, a number of examples will now be described.

Example 1

Ingredient	Amount
Carprofen	25g
Butylated hydroxytoluene	1g
Ethanol	100mL
Polyethylene glycol 400	qs 500mL

Example 2

Ingredient	Amount
Carprofen	10g
Butylated hydroxyanisole	2g
Sorbitol 70% aqueous solution	qs 500mL

Example 3

Ingredient	Amount
Carprofen	10g
Butylated hydroxytoluene	1g
Sorbitol 70% aqueous solution	100mL
Propylene glycol	qs 500mL

Example 4

Ingredient	Amount
Carprofen	25g
Butylated hydroxyanisole	2g
Polyethylene glycol 400	400mL
Ascorbic acid	5g
Ethanol	qs 500mL

Example 5

Ingredient	Amount
Carprofen	20g
Propylene glycol	qs to 1L
Benzyl alcohol	10g

Example 6

Ingredient	Amount
Carprofen	20g
Butylated hydroxytoluene	5g
Ethylene glycol	qs to 1L

Example 7

Ingredient	Amount
Carprofen	20g
Benzyl alcohol	10g
Butylated hydroxytoluene	2g
Propylene glycol	qs to 1L

In Examples 1-7, each composition was prepared by dissolving the carprofen in the polyol. The stabilising agent was then dissolved and if appropriate, co-solvent was added to complete the formulations. The availability of all of the ingredients used in Examples 1-7 is set out in Table 1.

Stability Study

The stability of the compositions described in Examples 3, 6 and 7 was evaluated by storing samples for various times at 30 and 40°C. The results of these stability trials are set out in Tables 2-4 from which it can be seen that the samples were stable for the time tested. By comparison, an example tested that did not incorporate a stabilising agent, had degraded to an unacceptable level of carprofen after 1- 3 months storage at 30°C.

Example 8 - Bioequivalent Study

A bioequivalence study in dogs of carprofen formulated as a liquid composition according to Example 7 (containing 20 mg carprofen/mL) to Rimadyl® tablets (20 mg per tablet; Pfizer Animal Health) after oral administration at 4 mg/kg was evaluated by the pharmacokinetic parameters area under the plasma concentration-time curve to infinity ($AUC_{0\text{-}inf}$), and maximum drug concentration (C_{max}).

Study Design

Twelve healthy adult dogs (6 Male, 6 Female) were orally dosed at 4 mg carprofen/kg body weight with each of the test and reference formulations in a randomised cross-over design with a 14 day washout period. Blood samples were drawn before and at prescribed intervals after dosing. Plasma was separated from the blood, then frozen and stored until it was analyzed for total racemate carprofen concentration by LCMSMS. Plasma concentration versus time data was analysed using bioequivalence comparison according to the method of Westlake as implemented in WinNonlin version 2.0 (Pharsight Corp, USA).

Study Results

Plasma harvested from the blood samples was frozen prior to transport for carprofen analysis. Comparison of the average plasma carprofen concentration versus time profiles of Carprofen Liquid versus Rimadyl® tablets is shown if Figure 1. Time to maximum concentration (Tmax), maximum concentration (Cmax), and area under the curve (AUC) were calculated for individual animals from the plasma carprofen concentrations and compared for the two formulations. With respect to $AUC_{(0\text{-}inf)}$, the confidence interval for Carprofen Liquid was within 80-120% of the confidence interval for Rimadyl® Tablets, and therefore met the criteria for bioequivalence. The comparison for Cmax, however, fell outside the interval defined for bioequivalence,

even though by ANOVA the effect of formulation on Cmax was not significant ($p = 0.5557$). The power for the C_{max} comparison was low (0.34), and it is likely if more animals had been included in the study, bioequivalence as determined by C_{max} would have been demonstrated.

Carprofen Liquid administered orally to dogs at a dose rate of 4 mg carprofen per kg body weight was found to be bioequivalent to Rimadyl Tablets with respect to $AUC_{(0\text{-inf})}$ as indicated by plasma carprofen concentrations. The two formulations were not quite bioequivalent with respect to Cmax.

Table 1 – Ingredient Availability

Ingredient	Available from
Carprofen	Pacific Resources International Pty Ltd
Butylated hydroxyanisole	Bronson & Jacobs
Polyethylene glycol 400	Bronson & Jacobs
Ascorbic acid	Bronson & Jacobs
Ethanol	CSR
Butylated hydroxytoluene	Bronson & Jacobs
Sorbitol	Bronson & Jacobs
Propylene glycol	Bronson & Jacobs
Benzyl alcohol	Bronson & Jacobs
Ethylene glycol	Bronson & Jacobs

Table 2 – Stability Evaluation of Example 3

Storage Time (months)	Carprofen (g/L) Temperature 30°C	Carprofen (g/L) Temperature 40°C
Initial	19.8	19.8
3	19.9	20.2
6	20.1	19.9
9	19.7	20.3

Table 3 – Stability Evaluation of Example 6

Storage Time (months)	Carprofen (g/L) Temperature 30°C	Carprofen (g/L) Temperature 40°C
Initial	21.0	21.0
3	21.0	21.0
6	20.6	20.6
12	20.0	19.8

Table 4 – Stability Evaluation of Example 7

Storage Time (months)	Carprofen (g/L) Temperature 30°C	Carprofen (g/L) Temperature 40°C
Initial	21.5	21.5
2	20.9	20.6
3	21.0	21.1
6	20.6	20.0
9	19.9	19.3
12	19.8	19.2
18	19.6	Not tested

CLAIMS:

1. A stable solvent-based composition comprising:
a therapeutically effective amount of carprofen;
one or more polyols in an amount of from about 20 to 998g/L;
one or more stabilising agents in an amount of from about 0.1 to 50g/L; and
one or more co-solvents in an amount of from about 0 to 500g/L.

2. The carprofen composition according to claim 1 wherein the one or more polyols are selected from the group consisting of propylene glycol, glycerol, sorbitol, solid polyethylene glycols and liquid polyethylene glycols and mixtures of the foregoing; the one or more stabilising agents are selected from the group consisting of α tocopherol and salts thereof, ascorbic acid and salts thereof, methoxyphenol and derivatives thereof, trihydroxybenzoate and derivatives thereof, hydroquinone and derivatives thereof, methyl phenol and derivatives thereof, sodium metabisulfite and benzyl alcohol.

3. The carprofen composition according to claim 1 or claim 2 wherein the carprofen is in an amount of from about 1 to 500g/L.

4. The carprofen composition according to claim 3 wherein the carprofen is in an amount of from about 5 to 50g/L.

5. The carprofen composition according to any one of claims 1 to 4 wherein the one or more polyols are in an amount of from about 700 to 998g/L

6. The carprofen composition according claim 5 wherein the one or more stabilising agents are in an amount of from about 10 to 20g/L.

7. The carprofen composition according claim 5 or claim 6 wherein the one or more co-solvents are in an amount of from about 10 to 300g/L.

8. Use of a composition which comprises:
one or more polyols;
one or more stabilising agents; and optionally,
one or more co-solvents,
to stabilise carprofen and to facilitate the oral administration of a therapeutically effective amount of carprofen to a warm-blooded non-human animal.

9. Use of a therapeutically effective amount of carprofen which is solubilised in a composition which comprises:
one or more polyols;
one or more stabilising agents; and optionally,
one or more co-solvents.

in the preparation of a medicament for treating pain and/or inflammation in a warm-blooded non-human animal.

10. The use according to claim 8 or 9 wherein the one or more polyols are selected from the group consisting of propylene glycol, glycerol, sorbitol, solid polyethylene glycols and liquid polyethylene glycols and mixtures of the foregoing; the one or more stabilising agents are selected from the group consisting of α tocopherol and salts thereof, ascorbic acid and salts thereof, methoxyphenol and derivatives thereof, trihydroxybenzoate and derivatives thereof, hydroquinone and derivatives thereof, methyl phenol and derivatives thereof, sodium metabisulfite and benzyl alcohol.

11. The use according to any one of claims 8 to 10 wherein the carprofen is in an amount of from about 1 to 500g/L.

12. The use according to claim 11 wherein the carprofen is in an amount of from about 20 to 50g/L.

13. The use according to any one of claims 8 to 12 wherein the one or more polyols are in an amount of from about 700 to 998g/L

14. The use according claim 13 wherein the one or more stabilising agents are in an amount of from about 10 to 20g/L.

15. The use according claim 13 or claim 14 wherein the one or more co-solvents are in an amount of from about 10 to 300g/L.

16. A method of treating pain and/or inflammation in a warm-blooded non-human animal, the method comprising administering to the animal a therapeutically effective amount of carprofen which is solubilised in a composition which comprises:

one or more polyols;

one or more stabilising agents; and optionally,

one or more co-solvents.

17. The method of claim 16 wherein the composition is administered orally.

18. The method according to claim 16 wherein the one or more polyols are selected from the group consisting of propylene glycol, glycerol, sorbitol, solid polyethylene glycols and liquid polyethylene glycols and mixtures of the foregoing; the one or more stabilising agents are selected from the group consisting of α tocopherol and salts thereof, ascorbic acid and salts thereof, methoxyphenol and derivatives thereof, trihydroxybenzoate and derivatives thereof, hydroquinone and derivatives thereof, methyl phenol and derivatives thereof, sodium metabisulfite and benzyl alcohol.

19. The method according to any one of claims 16 to 18 wherein the carprofen is in an amount of from about 1 to 500g/L.

20. The method according to claim 19 wherein the carprofen is in an amount of from about 20 to 50g/L.

21. The method according to any one of claims 16 to 20 wherein the one or more polyols are in an amount of from about 700 to 998g/L.

22. The method according claim 21 wherein the one or more stabilising agents are in an amount of from about 10 to 20g/L.

23. The method according claim 21 or claim 22 wherein the one or more co-solvents are in an amount of from about 10 to 300g/L.

24. A stable solvent-based composition as hereinbefore described with reference to any one of Examples 1 to 7.

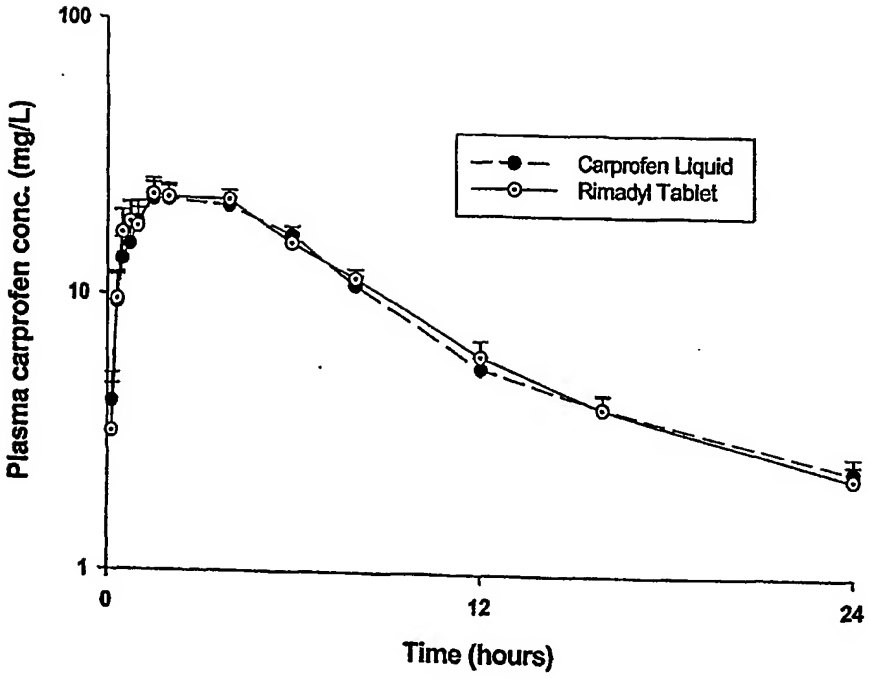
100
10
1
Plasma carprofen conc. (mg/L)
0
12
24
Time (hours)
Carprofen Liquid
Rimadyl Tablet

Figure 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2003/001729

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. [7]: A61K 031/403; A61P 29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
DWPI, Medline: carprofen, imadyl, rimadyl, PEG, glycerol, sorbitol, propylene glycol, polyethylene glycol

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	AU 31470/99 B2 (762464) (Boehringer Ingelheim Pharma KG) 26 June 2003 (& WO 1999/049845A1) See whole document	1, 3-9, 11-17, 19-24
X	WO 2001/060409A (Merial Limited) 23 August 2001 See whole document	1, 3-9, 11-17, 19-24
X	WO 2001/002015A (The University of Georgia Research Foundation) 11 January 2001 See whole document	1, 3-9, 11-17, 19-24

☐ Further documents are listed in the continuation of Box C ☒ See patent family annex

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

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Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/AU2003/001729

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report	Patent Family Member					
WO 9949845	AU	31470/99	BR	9909189	CA	2326048
	EP	0945131	EP	1066029	HU	0102036
	NO	20004822	NZ	507610	PL	342345
	US	6184220	US	6682747	ZA	200003951
WO 0160409	AU	33738/01	BR	0108449	CA	2400317
	CZ	20022772	EP	1263467	US	2003007958
WO 0102015	AU	42094/00	US	6368618		

END OF ANNEX